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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/234,290	01/20/1999	LINDA C. BURKLY	10274/008003	6288

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/234,290	Applicant(s) Burkly
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *25, 28, and 31-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25, 28, and 31-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Amendment filed September 11, 2001 (Paper No. 16) in response to the Office Action of March 9, 2001 (Paper No. 10) is acknowledged and has been entered. 25, 28 and 31-36 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claims 25, 28 and 31-36 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 10, Sections 7-8, pages 3-7 and in Paper No. 14, Sections 6-7, pages 3-4.

Applicant argues that (a) the statement in the specification that there has been little success in treating human diabetes does not apply to the instant application because the specification has demonstrated that specific inhibitors of VLA-4 VCAM effectively prevent immune cell destruction of pancreatic islet beta cells and thus could be used to therapeutically treat diabetes and that these inhibitors are not non-specific modalities, (b) applicant presented evidence that blocking the interaction of VLA-4 with one of its ligands is sufficient to significantly reduce the migration of immune cells to pancreatic islet beta cells and was sufficient to delay the onset of diabetes *in vivo*, (c) fibronectin and VCAM bind to VLA-4 and therefore fibronectin polypeptides provide an alternate method for blocking the VLA-4-VCAM interaction, (d) fibronectin polypeptides and fragments thereof were known inhibitors of VLA-4 activity and Applicant points to the specific binding sites, (e) the discovery of the present invention that blocking the VLA-4,VCAM interaction was sufficient to delay the onset of diabetes *in vivo* was unequivocally

established in the present application and since fibronectin polypeptides were known inhibitors of VLA-4 activity, the claimed invention is enabled, (f) specific dose ranges and modes of administration of fibronectin are provided in detail in the instant application and Examples 1-5 show the effectiveness of these doses which can be extrapolated to fibronectin, (g) the present invention showed that by specifically blocking one interaction, the VLA-4-VCAM interaction, it is possible to prevent immune cell destruction of pancreatic islet beta cells and the pathway is selective, (h) specificity can be achieved by adjusting the effective concentration of fibronectin,

The arguments have been considered but have not been found persuasive because (a') and (b') the specification has clearly demonstrated the unpredictability of diabetes treatment, in the absence of specific guidance and working examples drawn to a fibronectin polypeptide comprising the EILDV motif, no one of ordinary skill in the art would believe that it was more likely than not that the unpredictability of the art had been overcome by the instant specification, further, although the inhibitors are drawn to VLA-4-VCAM interactions, these actions are not specific to diabetes or to prediabetes for the reasons previously set forth, (c') Applicant does not provide objective evidence that fibronectin blocks VLA-4-VCAM interaction, just because one molecule binds to another, it does not mean that molecule blocks the binding of other molecules as discrete binding sites are well known in the art, (d') it is clear that the exemplified VCAM inhibitors and fibronectin act by different mechanisms and given the unpredictability of the art, in the absence of working examples, the invention is not enabled, further, for the reasons previously set forth fibronectin polypeptides and fragments thereof are not

enabled, (e') Applicant is arguing limitations not recited in the claims as presently constituted and for the reasons set forth previously and above, the claimed invention is not enabled, (f') a review of page 13 lines 4-26 and Examples 1-5 reveal that the teaching is not drawn to fibronectin and the specification does not teach how to extrapolate those dosages to fibronectin so that the invention will function as claimed, (g') Applicant is arguing limitations not recited in the claims as presently constituted, further, although selective, the targeting is not specific, (h') Applicant is arguing limitations neither recited in the claims as presently constituted nor described or recited in the specification as originally filed. Applicant's arguments have not been found persuasive and the rejection is maintained.

5. Claims 31 and 32 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 10, Section 10, pages 10-11 and Paper No. 14, Section 9, page 5.

Applicant traverses the rejection on the same grounds stated in Applicant's previous amendment. The arguments have been considered but have not been found persuasive for the reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 25, 28 and 31-36 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 14, Section 10, pages 5-6.

Applicant argues that it is clear from the claim that the phrase refers to a broad range of stages of diabetes and that prediabetic and mammals having partial beta cell destruction are included in this phrase. The argument has been considered but has not been found persuasive because, in the absence of a specific definition of

type I diabetes in the specification that includes prediabetic and mammals having partial beta cell destruction, it is assumed for examination purposes that the Type I diabetes claimed is the art recognized and specification defined Type I diabetes which is a disorder of carbohydrate metabolism, characterized by hyperglycemia and glyocuria and resulting from inadequate production or utilization of insulin. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 25, 28 and 31-36 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 14, Section 11, pages 6-12.

Applicant states that Examiner states that "because the specification, while being enabling for a prophylactic method of delaying IDD diabetes .....". It is noted that Examiner's statement is preceded by the proviso that because of the indefinite nature of the claim language, scope issues will be address in this rejection because, if Applicant were able to overcome the enablement rejections above, the claims would still be rejected under 35 USC 112 first paragraph for the reasons set forth. There is no statement in Examiner's action that suggests that the specification is enabling for a prophylactic method of delaying IDD diabetes in the absence of overcoming the previous rejections.

Applicant argues that (a) Applicant provides working examples showing a delay of onset of diabetes as well as a reference by Yang et al disclosing delay of onset of diabetes in NOD mice, (b) the term "prediabetic is intended to mean an individual at risk for the development of diabetes disease and the term "diabetic is intended to mean an individual with overt hyperglycemia and the term "prediabetic as used in the claims refers to the treatment of an individual at risk of having

diabetes at a stage prior to overt symptoms and thus the pending claims are commensurate in scope with the claimed invention, (c) the specification does enable a method of treating a mammal having partial beta cell destruction since Applicant has shown that inhibition of VLA-4-VCAM interaction prevented immune cell recruitment and thereby destruction of pancreatic islet beta cells, (d) Yang et al shown that treatment of NOD mice after the onset of insulitis from 10-14 weeks of age with VLA-4 antibody resulted in significant and long lasting suppression of ongoing and late stages of disease, thus the present invention also enables methods of treating ongoing disease, (e) Applicant repeats that the statements in the specification drawn to lack of success in treating IDD are misinterpreted by the Examiner and the Tisch reference is drawn only to antigen-specific immunotherapy which is irrelevant to the present application which is drawn to the successful prevention of immune cell recruitment to pancreatic beta cells using specific inhibitors of VLA-4-VCAM interaction, (f) NOD mice are predictive of the efficacy in the treatment of diabetes in man and NOD mice are an art recognized animal model for IDD. Many key features of IDDM are reflected in NOD mice and Bowman specifically sets out parallels between the human disorder and NOD mice. Applicant specifically quotes Bowman to support the contention that "NOD mouse..... provided a .....means with which to prevent the disease in humans", (g) Pozzilli et al teach that NOD mouse is one of the most appropriate models for preventing Type 1 diabetes.

The arguments have been considered but have not been found persuasive because (a') and (b') it is clear from both the specification and the claims that delayed onset of diabetes is not method of treatment of diabetes as defined by the

specification, (c') the claims are not drawn to preventing beta cell destruction but rather to treating diabetes, the evidence presented is not commensurate in scope with the claimed invention and for the reasons previously set forth, the invention is not enabled, (d') Applicant is arguing limitations not recited in the claims as presently constituted as the claims are not drawn to treatment with anti VLA-4 antibody but rather to a soluble fibronectin polypeptide, the evidence presented is not commensurate in scope with the claimed invention and for the reasons set forth previously and above, the invention is not enabled, (e') the statements in the specification are not misinterpreted but rather read broadly, further, Tisch states that the most critical factor in treating autoimmune disease is whether the therapy can be used to treat an ongoing autoimmune response or whether it is effective only in terms of prevention, the invention as claimed is not enabled for the reasons set forth previously and above and finally, Applicant is arguing limitations not recited in the claims as presently constituted, that is the claims are not drawn to the successful prevention of immune cell recruitment but rather to the treatment of IDD further, in view of the art recognized differences between NOD mouse and human, it can not be predicted that the invention will function as claimed based on the information in the specification or in the art, (f') Applicant is arguing limitations not recited in the claims as presently constituted, that is the claims are not drawn to preventing disease in humans, (g') although Pozzilli et al state that NOD mouse is one of the most appropriate models for this purpose, for the reasons previously set forth, it can not be predicted that the invention will function as claimed based on the information in the specification or in the art. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claim 36 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 14, Section 12, pages 12-14.

Applicant argues that at the time the present application was filed, the particular sites of fibronectin involved in the interaction with VLA-4 were known to be located in the alternate spliced IIICS or V region and that two distinct sites were recognized, since these locations were known and recognized in the prior art, Examiner is respectfully requested to reconsider and withdraw this rejection.

The argument has been considered but has not been found persuasive because the claims are not limited to the known recited sites and the invention is not enabled for the reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained. The rejection may be obviated by, for example, amending the claim to recite the known sites if support can be demonstrated in the specification as originally filed.

9. Claims 31 and 32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Section 10, Section 9, pages 8-9 and Paper No. 14, Section 8, pages 4-5.

Applicant argues that (a) blocking one interaction, the VLA-4-VCAM interaction, it is possible to effectively prevent immune cell destruction of pancreatic islet beta cells, (b) Applicant's repeats arguments drawn to general suppression, (c) Applicant repeats arguments drawn to affinity states of VLA-4 receptor. The arguments have been considered but have not been found persuasive (a') for the reasons previously set forth and above, further, Applicant is arguing limitations not recited in the claims as currently constituted, the method is not drawn to a method of preventing immune cell destruction of pancreatic islet beta

cells, (b') and (c') the arguments are not persuasive for the reasons previously set forth. Applicant's arguments have not been found persuasive and the rejection is maintained.

10. All other objections and rejections recited in Paper No. 13 are withdrawn.

11. No claims allowed.

12. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar
Primary Patent Examiner
November 12, 2001